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Myopic Anisometropia: Ocular Characteristics and Aetiological Considerations

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Abstract

Anisometropia represents a unique example of ocular development where the two eyes of an individual, with an identical genetic background and seemingly subject to identical environmental influences, can grow asymmetrically to produce significantly different refractive errors. This review provides an overview of the research examining myopic anisometropia, the ocular characteristics underlying the condition and the potential aetiological factors involved. Various mechanical factors are discussed including; corneal structure, intraocular pressure and forces generated during near work that may contribute to anisomyopia development. Potential visually guided mechanisms of unequal eye growth are also explored, including the influence of astigmatism, accommodation, higher order aberrations and the choroidal response to altered visual experience. The association between binocular vision, ocular dominance and asymmetric refraction is also considered, along with a review of the genetic contribution to the aetiology of myopic anisometropia. Despite a significant amount of research into the biomechanical, structural and optical characteristics of anisometropic eyes, there is still no unifying theory which adequately explains how two eyes within the same visual system grow to different endpoints.

Previous studies of both animals and humans have shown that refractive error is largely determined by axial length and that ocular growth is influenced by visual experience.¹ While there is evidence to suggest a genetic influence in the development of refractive errors (in particular myopia),^{2,3} it is now generally accepted that environmental factors such as near work⁴⁻⁶ and outdoor activity⁷ also play a significant role. However, there is currently no single theory that adequately explains the physiological mechanisms underlying the development of myopia. Commonly proposed hypotheses of potential mechanisms leading to myopia development include those where mechanical or optical factors promote excessive axial eye growth.

Myopic anisometropia or anisomyopia typically defined as a between eye difference in myopic spherical equivalent refractive errors of ≥ 1.00 D (usually due to an interocular asymmetry in axial lengths)⁸ is a unique refractive condition in which the fellow eyes of an individual have grown to two distinctly different end points. The investigation of anisometropia in myopia research (i.e. comparing the more myopic eye to the fellow relatively less myopic eye within the same individual) allows for potentially novel insights into the mechanisms underlying refractive error development since it allows for; greater control of potential confounding variables such as age and gender, minimisation of inter-subject variations in genetic and environmental factors, and thus provides an increased sensitivity in detecting a between subject (eye) difference in a variable of interest. The aim of this review is to summarise the literature regarding myopic anisometropia (primarily non-amblyopic anisometropia), with a specific focus on the optical (e.g. accommodation and higher order aberrations) and mechanical characteristics (e.g. corneal structure, intraocular pressure and forces generated during near work) of anisomyopia, which may provide further insight into the genesis of myopic refractive errors.

CHANGES IN ANISOMETROPIA THROUGHOUT LIFE

Numerous studies have examined the prevalence and magnitude of anisometropia at various stages throughout life. Figure 1 (based on the data from a large clinical population⁹) illustrates the typical changes observed from early childhood to older age; a decrease in the prevalence of anisometropia occurs during infancy and an increase throughout childhood and in older age groups. The change in the magnitude of anisometropia follows a similar trend, with an interocular difference ≥ 1.00 D (or an asymmetry in axial length $> \sim 0.3$ mm) being outside the typical range of anisometropia observed across all ages (0.00 - 0.75 D). The hypotheses related to the underlying mechanisms governing such age related changes in anisometropia are discussed in the following section.

Infancy and amblyopic anisometropia

The subject of amblyopic anisometropia is outside the scope of this paper (for review see Barrett et al¹⁰). However in this sub-group of amblyopic anisometropes the change in refraction of hyperopic, astigmatic and strabismic anisometropes does provide some insight regarding the development of asymmetric refractive errors.

Abrahamsson et al¹¹ followed 310 astigmatic one year olds (≥ 1.00 D in one eye) over a 3 year period and observed that large amounts of anisometropia can diminish during infancy. Anisometropia persisted in 46% of the anisometropic infants throughout the study period, and approximately 25% of these children developed amblyopia. In another study, Abrahamsson and Sjostrand¹² retrospectively examined the change in refraction of 20 children who had marked anisometropia ≥ 3 D at one year of age. Thirty percent of these children experienced an increase in the magnitude of their anisometropia (mean 1.4 D) and developed amblyopia between the ages of 3 to 10 years. Anisometropia decreased in the remaining 70% of children over time. Half of these children had a significant decrease in anisometropia (mean 3 D) and did not

develop amblyopia. However, the other half of this cohort experienced only a mild decrease in anisometropia (mean 1.2 D), but all of these children developed amblyopia.

A number of studies have also observed that the change in refraction over time varies between the amblyopic and non-amblyopic eyes of strabismic^{13,14} and non-strabismic¹⁵ children, with the non-amblyopic eye typically undergoing a significantly greater myopic shift. Caputo et al¹⁶ retrospectively reviewed the change in cycloplegic refractions of 46 young myopic anisometropes, more than half of whom had an eye movement disorder. The authors observed that the less myopic eye at the initial examination became more myopic over time, whereas the more myopic eye (often with amblyopia or strabismus) had a relatively stable refraction during development.

In summary, in early childhood, anisometropia typically decreases during emmetropisation (the reduction in neonatal refractive error towards emmetropia through coordinated eye growth) with the development of binocular coordination. When anisometropia persists beyond three years of age, it typically results in amblyopia. The refractive error of amblyopic eyes (associated with hyperopic anisometropia, strabismus or dysfunctional binocular vision) remains relatively stable over time, whereas fellow non-amblyopic eyes tend to undergo a myopic shift during youth. This suggests that clear vision and possibly accommodation (which is impaired in amblyopia^{17,18}) are required for successful emmetropisation and potentially also for myopia development. Dysfunctional or compromised binocular vision may also be related to the development of asymmetric myopic refractive errors.

Non-amblyopic anisometropia in childhood

Several longitudinal studies have examined the development of anisometropia during childhood and typically report an increase in the magnitude of interocular difference in refraction with age which is proportional to the increase in myopia (Figure 2). It has been suggested that divergent refractive errors between fellow eyes during childhood

associated with myopia development and progression are the result of a failure of internal (between eye) homeostatic mechanisms regulating symmetrical eye growth.²⁴ However, deliberate unilateral optical interventions in young children²⁵⁻²⁸ which result in asymmetric eye growth (discussed in detail later) suggest that a local vision dependent mechanism may also play a role in the development of anisometropia in youth.

The Ojai longitudinal study²⁹ followed the refractive development of children from age 6 to 17 years. Of 359 children with at least 22 refractive time points (over an 11-12 year period), 2.5% developed myopic anisometropia (≥ 1.00 D SER). In this first study examining the development of non-amblyopic myopic anisometropia during childhood, Hirsch stated that “...any theory for the development of myopia must explain how two eyes in an individual attain different refractive states, since both eyes accommodate and converge similarly, receive the same hormonal influences, perform the same tasks and have many other similarities”.

Parssinen²⁰ followed the change in refraction of 238 myopic children aged 9-11 years over a 3 year period and found that anisometropia remained stable in 67%, increased in 27% and decreased in 6% of subjects. As myopia increased over time (mean SER changed from -1.43 to -3.06 D), the magnitude of spherical equivalent anisometropia increased from 0.30 to 0.51 D. The initial refractive error, magnitude or axes of astigmatism and type of spectacle correction (single vision or bifocal) were not related to the change in anisometropia. However, the development of anisometropia correlated with the increase in myopia. The authors suggested that the greater the disruption in emmetropisation, due to either genetic or environmental factors, the greater the potential for an asymmetry in eye length to develop.

In a cohort of predominantly emmetropic Japanese schoolchildren (initial mean SER +0.91 D), Yamashita et al²³ also observed that spherical anisometropia remained relatively stable over a five year period (mean approximately 0.25 D) from age 6-11 years. Over the study period, anisometropia remained stable in 84% of children, while in 16% the magnitude increased or decreased with age. The interocular difference in

the magnitude of astigmatism was also stable over time (mean approximately 0.32 D) however, there was a significant positive correlation between the magnitude of spherical and astigmatic anisometropia. The interocular difference in astigmatism could potentially be a factor contributing to the development of spherical anisometropia or may be a consequence of asymmetric eye growth.

In a three year longitudinal study of almost two thousand children in Singapore aged 7 to 9 years, Tong et al²² found the mean spherical equivalent anisometropia increased slightly over time; from 0.29 D at baseline to 0.44 D at study completion. Less than 4% of children had anisometropia of 1.0 D or more at baseline. Of these children with 1.0 D or more of anisometropia, 5.1% had an increase in anisometropia of at least 0.5 D, whereas 3.4% had a decrease of at least 0.5 D. The change in anisometropia correlated with the change in inter-eye axial length. Compared with isometric children, each eye of the anisometric children had a higher rate of myopia progression, but the change in anisometropia over time was similar between the two cohorts.

Pointer and Gilmartin²¹ retrospectively examined the longitudinal change in refraction of a slightly older population aged 6-19 years. They compared the rate of refractive change in 21 unilateral myopic anisometropes (one eye myopic, fellow eye emmetropic) to an age matched control group of bilateral myopes. The rate of progression in the myopic eye of anisometropes was not significantly different to the rate of progression in bilateral myopes, the opposite trend to that reported by Tong et al.²²

Recently, Deng and Gwiazda¹⁹ examined the change in anisometropia during a longitudinal study of children from the age of 6 months to 12-15 years. The magnitude of anisometropia increased over time and was associated with an increase in both myopic and hyperopic refractive errors. This suggests that mechanisms other than excessive eye growth during childhood may promote the development of anisometropia (for example changes in binocular vision or ocular dominance).

The magnitude of anisometropia in children with active accommodation could potentially vary depending upon the method used to assess refractive error. However, there is evidence to suggest that the use of cycloplegia during the determination of refractive error has minimal influence upon the magnitude and prevalence (less than 1% difference in prevalence between cycloplegic and non-cycloplegic techniques) of anisometropia in both children³⁰ and adults³¹ of varying refractive errors.

In summary, the prevalence and magnitude of anisometropia typically increases steadily throughout childhood to young adulthood in association with age (Figure 2) and an increase in myopic or astigmatic refractive error. Changes in anisometropia during childhood correlate with asymmetric changes in axial length between the fellow eyes. The evidence regarding the rate of myopic progression in anisometropic eyes compared to isometropic eyes is conflicting.

Myopic Anisometropia in Adulthood

While anisometropia decreases during the early years of life (presumably through emmetropisation and binocular vision development) and increases during childhood and adolescence (associated with myopia development), throughout middle age (approximately 30 - 50 years) the prevalence and magnitude of anisometropia remains relatively stable (Figures 1 and 3). This may be related to the stability of distance refraction during this period of adult life. However, later in life (beyond 60 years), there is a marked increase in the prevalence of anisometropic refractive errors.³¹⁻³⁵

It has been suggested that the increase in anisometropia in older adults may be a result of asymmetric cataract development or unilateral cataract extraction. However, studies restricted to phakic patients still demonstrate an increase with age and a higher proportion of anisometropia in patients with bilateral compared to unilateral cataract,³² and anisometropia is found to be significantly associated with age even after controlling for the presence of cataract.³⁶

Figure 3 illustrates the age related changes in magnitude and prevalence of anisometropia for a large cohort of myopic subjects (refractive surgery candidates) excluding cases of pathology such as unilateral cataract (based on the data of Linke et al³¹). While this study has fewer younger (< 20 years) and older (> 60 years) subjects compared to the analysis of Qin et al⁹ (Figure 1), the data display an increase in the prevalence of anisometropia into old age in healthy eyes without pathology.

Weale³⁴ collated data from several studies examining the association between the prevalence of anisometropia and age and observed an approximate increase in prevalence of 1% for every seven years of life. He suggested that an asymmetry in cataract development could not explain the significant increase in anisometropia and suggested that neuro-senescence, or a breakdown in binocular vision may play a role in the genesis of divergent refraction in the later years. A recent study has shown that the prevalence of binocular vision disorders does increase significantly in older age groups.³⁷

In summary, the prevalence and magnitude of anisometropia varies throughout life. Studies of large clinical populations over a wide range of age groups and refractive errors have shown that while anisometropia is associated with spherical ametropia and astigmatism, it is also independently associated with age. A rapid decrease in anisometropia is observed during the early years of life, followed by an increase from childhood to adulthood. Anisometropia is typically stable in adulthood, but increases significantly in prevalence in older age. The increase observed later in life may be related to a regression of neural control of binocular vision. The increase in the prevalence and magnitude of anisometropia during the period of life typically associated with the onset and development of myopia is of particular interest, as understanding the mechanism underlying the development of anisometropia may provide insight into the development of myopia.

GENETICS AND ANISOMYOPIA

While numerous studies have investigated the influence of genetics on the development of myopia (e.g. familial studies,^{38,39} twin studies,^{2,3} identification of genetic loci in high myopia⁴⁰), relatively few studies have examined the heritability of anisometric refractive errors. In an early genealogical study, Goldschmidt⁴¹ investigated the immediate family of thirty-six teenagers with high myopia (greater than 6 D in one eye), nine of whom had moderate to severe unilateral myopia (average 8 D, range 4 - 14 D). None of the siblings of the anisometric probands displayed significant asymmetric refractive errors. Also, the refractive status of parents varied considerably; with 55% showing emmetropia or low hyperopia, 22% with isometric myopia, 11% with myopic anisometropia and 11% with antimetropia. Based on these findings, Goldschmidt⁴¹ concluded that unilateral high myopia does not “*conform to a simple, monomeric mode of inheritance*” and speculated that environmental factors may also influence the symmetry of refraction between the fellow eyes.

A number of other studies have also examined the pedigree of myopic anisometropes, with conflicting findings. Ohguro et al⁴² observed an autosomal dominant inheritance pattern in a young male with 20 D of anisomyopia. More recently, Feng et al⁴³ reported an autosomal-recessive inheritance pattern in a Chinese family with myopic anisometropia of approximately 5 D. However, in a study of 48 anisometric children, Weiss⁴⁴ reported that three female patients had a strong family history of anisomyopia and suggested an x-linked recessive inheritance pattern existed in cases of unilateral high axial myopia.

Several case reports of young monozygotic and dizygotic twins also suggest that genetics may play a role in the aetiology of moderate to severe myopic anisometropia (approximately 8 - 10 D). Mirror-image (*Sibling 1 refraction: R-L ∞ Sibling 2 refraction: L-R*) or directly symmetric (*Sibling 1 refraction: R-L ∞ Sibling 2 refraction: R-L*) severe anisometropia has been observed in both twins⁴⁵⁻⁴⁷ and non-twin siblings.^{48,49} Such high levels of anisometropia are typically due to abnormal ocular development in the

affected eye such as optic nerve hypoplasia⁴⁵, macular hypoplasia⁴⁷ or coloboma⁴⁸ or are associated with significant pathology such as chorioretinal atrophy.⁵⁰

Conversely, Angi et al⁵¹ observed two cases of discordant anisometropia in young monozygotic twins (i.e. anisometropia in one twin only). Asymmetries in refractive astigmatism were also observed in each of the affected (anisometropic) twins with a higher degree of astigmatism in the more myopic eye. The authors hypothesised that asymmetric visual deprivation due to uncorrected astigmatism during the preschool years directly influences anisomyopia development. In a pair of older monozygotic twins (62 years old), Dirani et al⁵² also observed significant discordant anisometropia (8 D of anisomyopia in one twin only). Given the identical genetic makeup and the absence of any ocular pathology or significant astigmatism, the refractive asymmetry between the twins might be a result of environmental factors such as trauma during embryonic development, injury during birth or incomplete genetic penetrance.⁵³

While conflicting evidence exists from familial studies regarding the inheritance of myopic anisometropia (which potentially suggests a multifactorial mode of inheritance); moderate to severe anisometropia present from a young age appears to be a result of genetic rather than environmental influences. Such cases of anisometropia are typically associated with a unilateral structural abnormality causing excessive axial elongation. However, in the absence of ocular pathology, it is likely that anisomyopia is a result of a combination of genetic and environmental factors such as abnormal (asymmetric) visual experience.

To date, no studies have specifically examined the role of genetics in the development of lower levels of myopic anisometropia, which are more commonly encountered.

However, recent advances in genetic testing which have enabled the identification of numerous genetic loci associated with myopic refractive errors⁵⁴⁻⁵⁷ could also potentially provide new insights into the genetic contributions to anisometropic refractive errors.

OCULAR CHARACTERISTICS OF ANISOMETROPIA

In this section we discuss the anatomical differences between the fellow eyes of anisometropes and speculate how such differences may come about or potentially influence the development and progression of anisomyopia. A number of studies have examined the various structural elements of anisometric eyes (Table 1). Briefly, the primary biometric basis of anisometropia is the between eye difference in axial length, in particular the vitreous chamber depth (Figure 4).

There appears to be minimal contribution from the anterior segment including corneal thickness, anterior chamber depth or crystalline lens thickness (except in lenticular anisomyopia associated with cataract⁶⁶), suggesting that anisometropia is primarily an interocular asymmetry in the magnitude or rate of posterior eye growth. A number of studies have also reported on the ocular characteristics in anisometric amblyopia with the asymmetry in refractive errors also being primarily axial in nature¹³ (but may also involve interocular differences in the cornea^{68,69} or crystalline lens structure⁷⁰) and has also been associated with alterations in optic nerve head morphology.^{71,72} Some debate still exists as to whether higher order aberrations play a role in the genesis of amblyopic anisometropia.⁷³⁻⁷⁷

MECHANICAL CONSIDERATIONS IN ANISOMYOPIA

If mechanical factors contribute to anisometric eye growth, then differences may be apparent in the biomechanical properties between the fellow eyes such as corneal thickness, corneal hysteresis or intraocular pressure (IOP). This section summarises the literature on the between eye symmetry of biomechanical factors in anisometropia and discusses potential mechanically driven pathways of asymmetric axial elongation.

Cornea

An early study examining the between eye symmetry of corneal thickness with an electronic digital pachometer revealed that both epithelial and stromal corneal thickness is similar between the fellow eyes of hyperopic and myopic anisometropes (mean absolute anisometropia 3.33 ± 3.15 D; 1-2 μm interocular corneal thickness differences).⁷⁸ This finding has also been confirmed using more recent technology (optical coherence tomography [OCT]) in severe levels of anisomyopia (~10 D, with less than 3 μm interocular difference in central corneal thickness).⁷⁹

While corneal thickness appears highly symmetrical between the fellow eyes of anisometropes, Xu et al⁷⁹ observed a small but statistically significant reduction in corneal hysteresis (1.00 mmHg) in the more myopic eye of severe anisometropes (mean anisometropia > 10 D), suggesting a slight change in the cornea's mechanical properties. Hysteresis is also reduced in conditions associated with corneal thinning such as advanced keratoconus or following corneal laser refractive surgery.⁸⁰ Shen et al⁸¹ also observed significantly lower levels of corneal hysteresis in high myopes (SER > -9.00 D) compared to a control group of emmetropes and low myopes with similar corneal thickness and suggested that corneal collagen structure may be altered with higher levels of myopia similar to the changes in scleral composition and biomechanics observed in high myopia.^{82,83} Conversely, in lower levels of myopic anisometropia (~2 D) corneal biomechanics appear to be unaltered between the fellow eyes.⁶² These studies suggest that changes in corneal structure or biomechanics appear to be limited to high levels of myopic anisometropia.

Intraocular pressure

Another potential mechanical factor in myopia development is the eye's intraocular pressure (IOP). The role of IOP in myopia development has been studied extensively in both animals and humans; however the findings have been equivocal. Since myopia is primarily axial in nature, early theories proposed that raised IOP was responsible for excessive inflation or elongation of the globe. Van Alphen⁸⁴ demonstrated that

increasing IOP in both enucleated cat and human eyes resulted in significant axial elongation of the globe without radial expansion. The author concluded that the tone of the ciliary muscle mediates the tension within the choroid and subsequently the sclera, which in turn influences expansion of the globe and leads to an increase in axial length. Since the measurement of IOP may be influenced by variables such as age, blood pressure, corneal thickness⁸⁵ and diurnal variation,⁸⁶ a number of studies have compared the more and less myopic eyes of anisometropes to control for individual variations, which may potentially confound results in comparative cohort studies investigating the association between IOP and different refractive errors (e.g. emmetropes compared with age-matched myopes) (Table 2).

If a relationship does exist between IOP and axial elongation, one might expect that IOP would be higher in the more myopic eye of anisometropes, at least during myopia development or progression. However, cross-sectional studies using both contact and non-contact applanation techniques have shown no significant differences in IOP between the fellow eyes of low-moderate level anisometropes (~2-5 D).^{62,87,89-91} These studies suggest that axial elongation due to a simple IOP induced expansion of the globe is unlikely to be involved in the development of axial anisomyopia. However, studies examining the symmetry of IOP in moderate to severe anisometropes (on average approximately 5-10 D anisomyopia)^{61,88} observed a slightly higher IOP (1-2 mmHg) in the more myopic eye, which approached⁷⁹ or reached^{61,88} statistical significance. An isolated case report of unilateral chronic angle closure in a young female described a marked myopic shift in the affected eye (8 D change in SER over eleven years), however, the asymmetric change in refraction was primarily due to altered corneal curvature (5.45 D interocular difference in mean corneal power) and not axial elongation (0.4 mm interocular difference).⁹²

However, it may also be possible that anisometropia could develop through an IOP dependent mechanism in the presence of symmetrical IOP, if between eye differences exist in scleral biomechanics. Lee and Edwards⁹⁰ calculated that the stress exerted

upon the sclera was significantly higher in the more myopic eyes of anisometropes compared to the fellow eye. The authors proposed that an interocular difference in scleral thickness due to different rates of collagen synthesis might result in asymmetric axial elongation and the development of anisomyopia despite symmetrical IOP.

While small, clinically insignificant differences in IOP have been detected between the fellow eyes of severe myopic anisometropes (~1-2 mmHg), in general, cross-sectional studies of anisomyopes do not support an IOP related mechanism of asymmetric axial expansion of the globe. The cross sectional nature of the above studies leaves open the possibility that either short-term (e.g. diurnal variations or IOP spikes⁹³) or longer-term fluctuations in IOP may vary in anisometric eyes. Although no studies have specifically reported on the change in IOP over time during the development of anisometropia, longitudinal studies of myopia development in children have failed to find an association between IOP and axial growth.^{94,95}

Mechanical effects of near work

Since a number of epidemiological studies^{4,96-98} have reported an association between near work and myopia, it has been suggested that mechanical forces generated during near work such as those produced during convergence, or ciliary muscle contraction could potentially promote axial elongation. When near work is performed the eyes typically converge and accommodate in order to maintain clear, single binocular vision of near targets. Here we consider potential mechanical pathways associated with convergence and accommodation in asymmetric myopia development.

Convergence

Forces exerted by the extraocular muscles during convergence are thought to have the potential to lead to changes in axial length.⁹⁹ Bayramlar et al¹⁰⁰ concluded that transient axial elongation associated with near work was a result of convergence rather than accommodation after observing significant vitreous chamber elongation measured

with ultrasound biometry in young subjects following near fixation with and without cycloplegia. However, Read et al¹⁰¹ reported that axial length measured with partial coherence interferometry appears largely unchanged in adults both during and following a period of sustained convergence.

Recently, Ghosh et al¹⁰² examined the influence of gaze direction (9 different directions were examined) upon axial length during distance fixation and also found no significant change in axial length with nasal gaze (i.e. convergence). However, a significant increase in axial length (relative to primary gaze) was observed during inferior and infero-nasal gaze directions. Importantly, axial elongation was only evident when the eye was turned to maintain fixation, rather than a head turn, suggesting that the changes in eye length were due to extraocular muscle forces. Interocular differences in the size or insertion points of the extraocular muscles, in particular those associated with convergence and downward gaze (i.e. the superior oblique and inferior rectus), or asymmetric convergence in downward gaze (one eye converging more than the fellow eye) as a result of an abnormal head turn could potentially result in different forces transmitted between fellow eyes and an asymmetry in transient axial length changes during near work.

It has also been suggested that anisometropia may be related to facial structure, specifically the position of the orbits. Lateral displacement of one orbit would induce an asymmetric convergence demand between the fellow eyes, potentially causing greater mechanical stress on the eye further from the vertical midline. Martinez¹⁰³ noted that anisometropes tended to have asymmetric naso-pupillary distances, however the interocular difference did not correlate with the magnitude or sign of the between eye difference in refractive errors. If convergent muscle forces do play a role in anisomyopia development, one might expect that in cases of unilateral esotropia the squinting eye would typically be myopic relative to the fixating eye. However, studies of strabismic children have found the opposite to be true (the fixing eye becomes more myopic relative to the squinting eye over time).¹³⁻¹⁵

Accommodation

Ciliary muscle contraction has also been found to be associated with small but significant increases in the eye's axial length. Various studies have documented transient changes in axial length using highly precise non-contact instruments during¹⁰⁴⁻¹⁰⁶ or following¹⁰⁷ periods of accommodation. However, the magnitude of axial elongation between myopic and emmetropic cohorts varies between studies.

In two separate studies of anisomyopes, no significant difference was observed between the fellow eyes with respect to transient axial length changes following a ten minute binocular reading task (2.5 D accommodation demand) or during an accommodation task at 2.5 and 5 D stimuli during monocular fixation.¹⁰⁸ While the more myopic eye displayed a slightly greater change in axial length during accommodation compared to the less myopic eyes for both the 2.5 D (3 μm greater) and 5 D stimuli (4 μm greater), these interocular differences did not reach statistical significance. Over time, or for larger accommodative demands, it may be possible that an asymmetric accommodative response could potentially lead to transient axial length elongation of different magnitude between the fellow eyes, potentially leading to axial anisometropia.

If ciliary body forces or choroidal tension generated during accommodation cause transient axial length changes following near work and are related to longer term changes in eye growth, then ciliary body (or ciliary muscle) thickness might be larger in myopes compared to emmetropes or larger in the more myopic eye of anisomyopes relative to the fellow eye. This finding has been reported previously in children (emmetropes compared to myopes)¹⁰⁹ and in cases of unilateral high myopia (mean anisometropia 8 D).¹¹⁰ However, in a recent study of anisometropes (≥ 1.00 D spherical anisometropia), ciliary muscle size was largely symmetrical between the fellow eyes (slightly thinner in the more myopic eye).¹¹¹

Factors other than ciliary body size may also influence the amount of force transmitted to the posterior eye during accommodation such as the structural and biomechanical properties of the choroid and sclera. Significantly thinner choroids have been observed in myopic children compared to emmetropes¹¹² and in the more myopic eyes of anisomyopic adults,⁶⁴ which could potentially promote unequal axial elongation (or at least result in asymmetric biomechanical stress at the posterior globe) in the presence of symmetrical ciliary body structure and function. On the other hand, it has also been suggested that a thicker ciliary muscle may restrict equatorial eye growth (producing greater axial expansion), or result in poor contractility leading to a reduced accommodative response, both of which could potentially initiate axial elongation and myopia development.¹¹³

In a retrospective case series examining long-term complications of unilateral traumatic hyphema, Lin and Lue¹¹⁴ observed significant anisometropia (≥ 1.00 D) in 44% of their patients. On average, the unaffected eye was 1.23 ± 2.13 D more myopic than the injured eye for all trauma patients and 2.76 ± 2.47 D for the subset of 'traumatic' anisometropes. A strong correlation was observed between the extent of anterior chamber angle recession (i.e. 0 - 360 degrees) and the between eye asymmetry in refraction ($r = 0.60$, $p < 0.01$) and axial length ($r = -0.57$, $p < 0.01$). Following trauma, the majority of patients also displayed an asymmetry in accommodation. Given that IOP was not significantly different between the fellow eyes; the authors suggested that "traumatic cycloplegia" halted myopia progression in the injured eye compared to the fellow eye, similar to the effect of atropine¹¹⁵ or pirenzepine.¹¹⁶ This study adds some weight to the theory that the ciliary body (or accommodation) is involved in asymmetric axial elongation. However, whether this is an optical or mechanical mechanism (or a combination of the two) remains unclear.

OPTICAL FACTORS IN ANISOMYOPIA

Numerous studies with animal models have shown that unilateral manipulation of visual input such as hyperopic defocus (via spectacle lens) or form deprivation (via lid suture or diffuser) results in compensatory eye growth (choroidal thinning and axial elongation to adjust the position of the retina) to achieve emmetropia in the experimentally treated eye.^{1,117,118} This results in the development of anisometropia (or unilateral myopia). If anisomyopic eye growth in humans is influenced by an interocular difference in visual experience, then asymmetries in optical properties (e.g. corneal or total ocular higher order aberrations) may be evident between the fellow eyes of anisometropes. In this section, we examine the literature on image mediated asymmetric eye growth in humans, and studies comparing the optical properties between the fellow eyes of anisometropes.

Asymmetric visual experience and eye growth

Deprivation of form vision during infancy results in the most severe form of amblyopia. Retinal image degradation due to ptosis,¹¹⁹ corneal scarring,¹²⁰ congenital cataract¹²¹ or vitreous haemorrhage¹²² typically leads to excessive axial elongation (form deprivation myopia) and dense amblyopia. The magnitude of myopia, and thus anisometropia, is related to the degree and age at the onset of image degradation.

Similarly, studies have shown that deliberate unilateral manipulation of the retinal image in humans can alter axial elongation between the fellow eyes. Cheung et al²⁶ observed asymmetric eye growth in an eleven year old myopic anisometrope undergoing unilateral orthokeratology treatment in the more myopic eye. Over a two year treatment period, the less myopic eye grew 0.34 mm (an increase in myopia of approximately 1 D) compared to the treated more myopic eye which grew only 0.13 mm, suggesting that the corneal reshaping slowed myopia progression in the treated eye. Similarly, in a contralateral design clinical trial of 26 children wearing an orthokeratology lens in one eye and a conventional RGP lens in the fellow eye, Swarbrick et al²⁸ observed a significant interocular difference in both eye growth and

refraction after one year; the eye wearing the conventional RGP lens was on average 0.09 ± 0.17 mm longer and 0.57 ± 0.66 D more myopic than the fellow eye wearing the orthokeratology lens.

Phillips²⁷ followed 13 eleven year old myopes fitted with monovision spectacles (≥ 2.00 D) over a period of thirty months. Using dynamic retinoscopy, the author observed that all children accommodated to read using the distance corrected dominant eye rather than the near corrected eye. As a result, the near corrected eye received myopic defocus for all levels of accommodation. Myopia progression was significantly slower in the near corrected eye compared to the fellow distance corrected eye. All subjects developed anisometropia due to the interocular symmetry in vitreous chamber growth (interocular difference of 0.13 mm/year). When these subjects returned to conventional distance spectacle wear, the anisometropia reduced to baseline levels within 18 months.

In a larger study, Anstice and Phillips²⁵ examined the change in refraction and axial length in 40 young non-anisometric myopes (11-14 years old) over a period of twenty months while wearing a different design of soft contact lens in each eye. A single vision lens was worn in one eye and a multifocal lens (simultaneous vision - distance centre) was worn in the fellow eye. The mean increase in myopia progression (spherical equivalent and axial length) over ten months was significantly reduced in the eyes wearing the multifocal lens (-0.44 ± 0.33 D and 0.11 ± 0.09 mm) compared to the single vision lens (-0.69 ± 0.38 D and 0.22 ± 0.10 mm). The reduction in myopia progression associated with multifocal lens wear was attributed to the constant peripheral myopic defocus induced during all levels of accommodation.

Recently, Read et al¹²³ examined the short-term change in axial length and choroidal thickness in young adults following one hour of imposed monocular defocus. Using an optical biometer, significant changes in axial length were observed which corresponded to the direction of the induced defocus. Lens induced hyperopic defocus (-3 D) and form deprivation (diffuser) both resulted in choroidal thinning and axial elongation, while

lens induced myopic defocus (+3 D) resulted in a thickening of the choroid and a decrease in axial length (only in the eye with the imposed defocus). This study suggests that the adult human visual system is capable of detecting the direction of defocus and adjusting the position of the retina to minimise the imposed blur by altering the thickness of the choroid. Previous studies with young animals have shown similar short term changes in choroidal thickness occurring within minutes in response to defocus that precede longer term changes in eye growth.

These studies demonstrate that deliberate manipulation of the focal properties of the retinal image in young subjects has the potential to influence eye growth and lead to changes in the refractive state of the eye. It follows that interocular differences in retinal focus may underlie anisomyopic eye growth.

A recent case report of non-amblyopic progressive adult antimetropia¹²⁴ (anisometropia in which one eye is myopic and the fellow eye is hyperopic) also adds weight to the above evidence for a local mechanism of eye growth regulation in humans with relatively independent control in each eye. In this particular case, the increase in antimetropia was due to a combination of unilateral axial elongation in one eye and the gradual manifestation of latent hyperopia in the fellow eye.

Sorsby et al⁸ reported on the ocular characteristics of six antimetropic children (aged 7 - 16 years). All of the children exhibited low hyperopia in one eye (1 - 2 D) and a moderate degree of myopia in the fellow eye (mean absolute anitmetropia 4.93 ± 1.33 D). The origin of the antimetropia varied substantially; three cases of axial length asymmetry (mean 2.44 ± 0.13 mm), two due to an interocular difference in crystalline lens power (mean 4.25 ± 0.48 D) and one as a result of an asymmetry in corneal power (1.7 D). Using more sophisticated techniques (ultrasonography and corneal topography), Kuo et al⁶¹ examined a larger cohort of older antimetropes of similar magnitude (19 - 30 years old, mean SER antimetropia 5.28 D) and found no significant differences between the fellow eyes for anterior eye biometrics (corneal thickness and

anterior chamber depth), but a significant difference in axial lengths (mean 2.00 mm, 95% CI 1.7 - 2.5 mm) and concluded that the biometric basis of antimetropia is the interocular asymmetry in axial length.

Antimetropic eye growth in the absence of amblyopia or pathology is an intriguing refractive anomaly, perhaps even more so than anisomyopia, since the two eyes within the one visual system have not only developed markedly different refractive errors, but in opposite directions from emmetropia. While the existing literature regarding antimetropia is limited (potentially due to its low prevalence, up to 0.1%^{125,126}), future research into antimetropic eye growth may provide valuable insights into retinal image mediated asymmetric eye growth and myopia development.

Pupil size

When considering the optical properties or image quality of the eye, an important factor to take into account is pupil size. Asymmetry in pupil size (anisocoria) or an interocular difference in the quality and size of the fundus reflex is often used as a screening technique for interocular differences in refractive errors or ocular misalignment in children.¹²⁷ However, in a cohort of anisomyopic subjects,¹⁰⁸ pupil dimensions were measured using digital photography and customised software and were found to be highly symmetrical between the more and less myopic eyes. Although the difference in pupil diameter between the more and less myopic eyes approached significance (more 3.53 mm and less 3.48 mm, $p = 0.09$) there was no correlation between the degree of physiological anisocoria and anisometropia.

Corneal power

It is generally accepted that in an individual with no eyelid abnormalities, the two eyes display some degree of corneal symmetry (direct or mirror symmetry) with respect to the axes of astigmatism.^{128,129} A high degree of symmetry exists between fellow eyes for corneal power in both isometropic eyes¹³⁰ and anisometropic eyes measured with

keratometry (i.e. the central cornea)^{58-60,63} (Table 3). Although there is significant variability in corneal power in emmetropia and myopia,¹³¹ several studies have shown greater corneal power¹³²⁻¹³⁴ and a less prolate corneal shape¹³⁵ in myopes compared to emmetropes.

Using videokeratoscopy, Vincent et al⁶² observed small interocular differences between the flat and steep corneal meridians of fellow eyes in a cohort of anisomyopes. The more myopic eyes exhibited more prolate corneas, in contrast to previous studies, which have shown that corneas tend to become less prolate with increasing levels of myopia.^{136,137} The mean refractive corneal power (average of the steep and flat corneal meridians) was also significantly greater (steeper) in the more myopic eyes which is in contrast with previous biometric studies of anisometropic subjects^{8,58,61} and may be due to the more accurate method used to assess the corneal shape.

Gwiazda et al¹³⁸ followed a cohort of children from an early age (1 year) and observed that infantile against the rule astigmatism was associated with increased myopia and astigmatism during childhood (school age) and hypothesised that uncorrected astigmatic errors during the emmetropisation period may play a role in the development of myopia.

Buehren et al¹³⁹ also postulated that altered mid-peripheral corneal shape and optics due to lid pressure during reading might be a potential trigger for refractive error development. Temporary corneal distortions (changes in corneal astigmatism or higher order aberrations) resulting in hyperopic defocus or retinal image degradation may lead to compensatory axial elongation. A similar mechanism could be proposed in the development of myopic anisometropia. A greater amount of peripheral corneal flattening in one eye could result in peripheral hyperopic defocus, triggering asymmetric axial elongation.

Vincent et al¹⁴⁰ investigated the change in corneal optics following a short reading task in young non-amblyopic anisomyopes. The more myopic eye displayed a small but significantly greater increase in against the rule astigmatism compared to the less

myopic eye over a 6 mm analysis diameter. This finding lends some support to the notion of an astigmatic image mediated mechanism associated with the development of anisomyopia.

However, it could also be argued that altered corneal shape may be a result of vision-dependent eye growth rather than a cause of myopia development. Kee and Deng¹⁴¹ reported significant changes in corneal astigmatism following various visual manipulations in young chicks including form deprivation, hyperopic and myopic defocus. Small corneal differences observed between the eyes of anisometric subjects may be attributed to axial elongation (rather than cause it) and subsequent alterations in scleral structure which could potentially impact upon the cornea at the limbus.

Together, these studies suggest that alterations in corneal optics could potentially play a role in the development of myopia and anisometropia. Given the association between the progression of astigmatism and anisometropia during childhood and the observation of higher levels of astigmatism in the more myopic eye of anisometric twins, the relationship between astigmatism, retinal image quality and asymmetric eye growth requires further research.

Accommodation

The accuracy of the accommodative response and optical effects of accommodation in various refractive error groups has been investigated in detail.¹⁴² Typically a greater lag of accommodation (under accommodation during near work) has been reported in myopes compared to emmetropes.¹⁴³⁻¹⁴⁶ It has been suggested that hyperopic defocus associated with a lag of accommodation may provide a cue to eye growth and myopia development.

A number of studies have explored the plausibility of aniso-accommodation in isometric individuals. Koh and Charman¹⁴⁷ reported that during binocular viewing, when the eyes are presented with stimuli of unequal accommodative demand, the eye

which requires the least accommodative effort to maintain clear focus of the target will control the accommodative response in both eyes. Marran and Schor¹⁴⁸ also observed that when presented with unequal accommodative targets, subjects demonstrated aniso-accommodation to approximately one quarter of the interocular difference in demands. However, at a stimulus difference of approximately 3 D there appeared to be a suppression mechanism involved in eliminating the image from the eye with the higher accommodation demand. Conversely, Troilo et al¹⁴⁹ suggested that the binocular accommodative response in marmosets reared with imposed anisometric defocus was an average of the two different demands rather than an aniso-accommodative mechanism or a response driven by the lower of the two demands. Thus, interocular differences in the accommodation demand (or response) could potentially provide a stimulus to asymmetric eye growth. Charman¹⁵⁰ postulated that the simple act of reading across a page induces an unequal accommodative demand between the eyes (when not viewing directly along the midline), which increases as the working distance to the text is decreased (or interpupillary distance increases). However, if the eyes remain relatively centred and stationary over the reading task, the defocus experienced in one eye will also be experienced in the fellow eye in the opposite direction of gaze, and each eye would receive the same amount of blur (averaged over time). When a head tilt or turn is adopted, or any position in which the reading material is not centred in front of the eyes, the accommodative demand for each eye will again change. At a working distance of 10 cm when reading on an A4 page, the interocular difference in accommodative demand at the end of a line of text may reach up to 2 D.¹⁵⁰ Therefore, viewing reading material at a short working distance (with a head tilt) may lead to hyperopic defocus in one eye, assuming a consensual accommodative response to the lower of the two demands.

In a qualitative study, Childress et al¹⁵¹ examined refractive error types in a range of occupations and considered the potential influence of specific work related visual tasks (with respect to the vertical midline) upon the development of anisometropia. The

authors questioned participants regarding their typical visual demands, in particular the position of reading material and work instruments. In general, those who reported a habitual reading posture centred on the vertical midline displayed symmetrical refractive errors (both spherical and astigmatic), while individuals who placed reading material to one side (due to office environment or job requirements) were more often anisometropic with the eye closer to the visual task usually the more myopic eye.

In a similar study, Harris¹⁵² investigated the association between the specific visual demands of different symphony musicians (i.e. the effect of instrument type on head tilt or turn and seat position relative to the conductor and sheet music) and their refractive errors. A number of musicians exhibited myopic and astigmatic anisometropia.

Typically, the eye positioned closer to the visual task at near displayed greater spherical myopia and less astigmatism compared to the fellow eye. The findings from these studies suggest a potential role for asymmetric viewing during near work in the development of anisomyopia; however, the underlying mechanism (e.g. unequal accommodative demands, eyelid forces or asymmetric convergence) remains unknown.

A limited number of studies have directly examined the accommodative response in myopic anisometropes (Table 4). In an early study, Hosaka et al¹⁵³ measured the monocular amplitude of accommodation in a large cohort of anisometropes (interocular difference ≥ 1.00 D and including some amblyopes) and a control group of isometropes. Ninety-seven percent of isometropes had an interocular difference in amplitude of accommodation of less than 2.00 D, compared to 69% in the anisometropic cohort. Of the anisometropic subjects with an interocular difference in accommodation greater than 0.5 D, the amplitude of accommodation was reduced in the more myopic eye 70% of the time. However, there was no significant correlation between the interocular difference in accommodative amplitude and the magnitude of anisometropia. Seventeen subjects (mean age 21 ± 7 years) exhibited an interocular difference in accommodative response between 2-3 D; but again, there was no clear

evidence of a refractive error-accommodation interaction (i.e. the more myopic eye showed a greater lag in only 50% of these cases).

Xu et al¹⁵⁴ used an infrared optometer to measure the interocular symmetry of the accommodative response in twenty anisometropes with 2.50 - 7.00 D of spherical anisometropia at a range of accommodative demands. The more myopic eyes exhibited a larger accommodative lag compared to the less myopic eyes for accommodation demands of 2, 3, and 4 D; however, these differences did not reach statistical significance.

Recently, Lin et al⁶⁵ investigated the magnitude of near work induced transient myopia (NITM, a slight myopic shift in refractive error following near work) in the more and less myopic eyes of young anisomyopes (~2 D anisometropia) during binocular viewing. On average, the more myopic eyes displayed a slightly greater level of NITM and a longer decay period to baseline refraction, which reached statistical significance. A moderate correlation was also observed between the interocular difference in NITM and the magnitude of anisometropia ($r = 0.31$, $p < 0.05$). The authors suggested that interocular differences in ciliary body thickness¹¹⁰ may be related to the observed differences in NITM between the fellow eyes. However, for this relatively low level of anisomyopia, ciliary body biometrics are similar between the more and less myopic eyes.¹¹¹

To our knowledge these are the only previous studies to directly examine the interocular symmetry of accommodation in anisomyopia. This may be due to previous research, which has shown a symmetric accommodative response between the eyes of normal subjects during both monocular¹⁵⁵ and binocular¹⁵⁶ viewing. It has been suggested that the dominant eye (traditionally the preferred eye for distant sighting) may exhibit different accommodative responses to the fellow non-dominant eye. In amblyopia, the non-dominant (amblyopic) eye shows impaired accommodation;^{76,157,158} however, few studies have examined the role of ocular dominance and accommodation in non-amblyopic subjects. Given the potential association between accommodation

and myopia development, the characteristics of accommodation between the dominant and non-dominant eyes are of interest with respect to refractive error development.

Higher order aberrations

Higher-order aberrations (HOA) are optical imperfections of the eye (excluding defocus and astigmatism) that degrade retinal image quality and may influence eye growth. Although the unaccommodated eyes of myopes and emmetropes exhibit similar levels of aberrations,^{159,160} during or following near work myopes tend to have higher levels of aberrations in comparison to their emmetropic counterparts.¹⁶¹⁻¹⁶³ Recent studies suggest this may be due to differences in the cornea or palpebral aperture morphology.^{162,164} Several studies have compared the higher order aberration profile between the fellow eyes of anisometropes, with conflicting results (Table 5).

Corneal higher order aberrations

In non-anisometric populations, there is a high degree of symmetry between the fellow eyes for measures of corneal aberrations.^{169,170} Plech et al⁷⁴ also observed that corneal higher-order aberrations were similar between fellow eyes in cases of unilateral amblyopia including isometric and anisometric refractive errors. In a population of non-amblyopic anisomyopes, Vincent et al⁶² found a high degree of interocular symmetry for corneal higher order aberrations, which increased as the corneal analysis diameter increased. This suggests that the optical quality of the cornea is similar for the two eyes of myopic anisometropes, which does not support a model of myopia development driven by corneal aberrations. However, these measurements were not taken during or following near work, which has been shown to alter corneal optics due to eyelid pressure. Using the same non-amblyopic anisomyopes, a further study¹⁴⁰ was conducted to examine the symmetry of the change in corneal optics following a short duration reading task. The changes in corneal higher order aberrations following reading were not significantly different between the fellow eyes, however, the more

myopic eyes exhibited a significantly greater increase in corneal against the rule astigmatism which resulted in a greater reduction in image quality over a 6 mm pupil diameter.

Total ocular higher order aberrations

A high degree of interocular symmetry also exists for the total HOA of the eye after correcting for enantiomorphism (between eye mirror symmetry) in various isometric populations during distance¹⁷¹⁻¹⁷⁵ and near fixation.¹⁷⁶ However, studies of chicks^{177,178} have reported a significant increase in higher order aberrations following monocular form deprivation and myopia development and recently Colletta et al¹⁷⁹ observed that experimentally form deprived eyes of marmosets had significantly higher levels of the asymmetric aberration trefoil compared to the fellow control eye. These animal models suggest that interocular asymmetries in higher order aberrations may be a result of asymmetric visual experience and/or eye growth, rather than a cause.

In a cohort of human anisomyopes (~3.40 D anisometropia) Kwan et al¹⁶⁵ also observed significant interocular symmetry in higher-order aberrations, however they also noted significantly higher levels of third order and total higher-order aberrations in the less myopic eye compared to the more myopic eye. Conversely, more recent studies examining lower levels of anisomyopia (~1.75 D anisometropia) have found a high degree of interocular symmetry (and no significant interocular differences) in individual higher order aberrations, 3rd order, 4th order and 5th order aberrations or total higher-order aberrations^{62,166} (Table 5, Figure 5). Retrospective clinical studies of total HOA in anisometropia also report a high degree of symmetry between the fellow eyes for almost all individual wavefront coefficients¹⁶⁷ or a higher degree of interocular symmetry in anisometropes compared to isometropes.¹⁶⁸

In summary, these studies (which generally captured aberration measurements during distance fixation) do not support the hypothesis that increased aberrations (and hence reduced retinal image quality) in the unaccommodated eye play a role in the

development of myopic anisometropia. However, this does not rule out the possibility that higher-order aberrations play a role in the development of myopia or anisometropia during or following near work, or that the sign of the aberrations (e.g. relative peripheral hyperopia) may play a role. Additionally, no longitudinal studies have currently been published examining the symmetry of higher order aberrations in children during myopia development.

THE POSTERIOR EYE IN ANISOMYOPIA

Structural alterations of the posterior eye such as staphyloma and optic disc abnormalities are often associated with high myopia and excessive axial elongation.¹⁸⁰ With recent advances in posterior eye imaging (OCT), more subtle changes in retinal and choroidal thickness have also been observed over a range of myopic refractive errors (typically a thinning of the retina and choroid with increasing levels of myopia).¹⁸¹⁻¹⁸³

Retina

While a number of studies have examined the interocular symmetry of retinal thickness in amblyopic anisometropia, few studies have examined retinal biometrics in myopic anisometropia. For lower levels of myopic anisometropia (1.5 - 3 D) there appears to be no obvious structural differences between the fellow eyes with respect to retinal thickness at the macula¹⁸⁴ or in paramacular regions⁶⁴ and the retinal nerve fibre layer thickness surrounding the optic nerve.¹⁸⁵ Additionally, a recent study examining retinal characteristics in severe myopic anisometropia (~10 D) found no significant differences between the fellow eyes for measures of foveal retinal thickness, but some retinal thinning was observed in the inferior and nasal paramacular regions in the order of 10-20 μm .¹⁸⁶

Logan et al⁵⁸ calculated the posterior retinal contour in Asian and Caucasian low myopic anisometropes of ~2 D (using peripheral refraction coupled with corneal

curvature and axial length data) and observed an ethnic influence upon interocular differences in posterior eye shape. Caucasians exhibited between eye differences in axial length that were greater nasally compared to temporally in the posterior retinal contour, while in anisometropes of Taiwanese-Chinese descent, the interocular difference in axial length was similar between corresponding nasal and temporal locations.

Choroid

Until recently, choroidal thickness had not been directly measured in anisometric eyes. Early studies estimated the interocular symmetry of choroidal blood flow in anisomyopes by measuring the ocular pulse amplitude (OPA) and the pulsatile ocular blood flow (POBF). Shih et al⁸⁹ observed that when anisometropia exceeded 3 D, there was a significant interocular ocular difference in the OPA (0.27 mmHg). Similarly, Lam et al⁹¹ found that in anisometric subjects (> 2.0 D) both OPA and POBF were significantly lower in the more myopic eye of axial anisometropes and the interocular difference in OPA and POBF were both significantly correlated with the interocular difference in axial length. These studies suggest that reduced choroidal blood flow is associated with increasing myopia.

Vincent et al⁶⁴ directly measured choroidal thickness in adult anisomyopes using OCT and observed significant interocular differences proportional to the degree of axial anisometropia. These differences (a thinner choroid in the more myopic eye) were more apparent in Asian anisometropes compared to Caucasians. This finding was consistent with the previous posterior retinal findings of Logan et al,⁵⁸ since Asians displayed relatively symmetrical interocular differences in choroidal thickness at corresponding nasal and temporal locations, while in Caucasians choroidal thinning was limited to a region nasal to the fovea of the more myopic eye. Together, these studies suggest that some of the structural changes in the eye associated with anisomyopia differ between Asian and Caucasian subjects.

Since previous animal studies have shown an active choroidal mechanism to emmetropise (by adjusting the position of the retina) to imposed defocus^{118,187} and evidence for a similar mechanism has been reported in humans,¹²³ it is possible that the choroid plays a role in the development of anisomyopia. Since the above study⁶⁴ was cross sectional it is unclear if the thinning of the choroid in the more myopic eye was a cause or consequence of myopia development. However, modelling suggested that the interocular differences observed were not accounted for by a simple passive stretching of the globe. This supports the theory that the between eye differences in choroidal thickness may be a result of an active ocular mechanism, similar to the response observed in monocular manipulation of refractive error in animal models.

OCULAR DOMINANCE

Several studies have investigated the association between ocular sighting dominance (the preference for the visual input from one eye when viewing binocularly) and anisometropia (Table 6). In a cohort of adult Asian myopes Cheng et al¹⁸⁸ observed that when the degree of anisometropia exceeded 1.75 D, the dominant eye was always the more myopic eye and hypothesised that an aniso-accommodative response (due to unequal accommodative demand during reading) may be responsible for the dominant eye being more myopic. Similarly, a study examining predominantly Asian myopic anisometropes found that when the magnitude of anisometropia exceeded 1.75 D, the more myopic eye was almost always the dominant sighting eye (90% of cases) and when anisometropia exceeded 2.25 D the more myopic eye was always the dominant eye.⁶² This finding is in agreement with studies of young amblyopic strabismic in which the fixating (dominant) eye typically undergoes a greater myopic shift during childhood compared to the fellow amblyopic eye.¹³⁻¹⁵

Conversely, in a study of Asian children, Chia et al¹⁸⁹ found no such association. The authors reported that when anisometropia was greater than 1.50 D, the dominant eye was more myopic in only 56% of subjects. A large retrospective study of over ten

thousand patients screened for refractive surgery in Western Europe³¹ (presumably a predominantly Caucasian/European cohort) also recently found that in myopic anisometropia the dominant eye is typically the eye with the lower refractive error. While these studies all employed similar techniques to determine ocular dominance (variations of the hole-in-the-card test¹⁹¹), differences in subject ethnicity and age may account for some of the discrepancies observed in the findings between the studies. In summary, cross sectional studies of adult myopes (of predominantly Asian ethnicity) have found that beyond a threshold level of anisometropia (1.75 - 2.25 D), the more myopic eye is typically the dominant sighting eye. However, studies of Asian children or European adults have observed that the non-dominant eye is typically the more myopic eye, or the eye with a greater level of astigmatism.

Retinal image quality and ocular dominance

In anisometropic amblyopia, the dominant sighting eye is typically the eye with better visual acuity, although there may be exceptions in some cases with intermittent strabismus.¹⁹² If visual acuity influences ocular dominance in myopic anisometropia, one might expect to see a significant difference in acuity between the fellow eyes of anisometropes, or a greater difference between eyes in acuity with increasing levels of myopic anisometropia. In non-amblyopic myopic anisometropes, no significant difference in visual acuity was observed between the fellow eyes for either high (> 1.75 D) or low levels of anisometropia (≤ 1.75 D).⁶² Furthermore, total higher order monochromatic aberrations (which alter the retinal image) were compared between the dominant and non-dominant eyes to examine if subtle optical differences between the eyes might somehow influence ocular dominance. However, the dominant and non-dominant eyes displayed similar root mean square (RMS) error values for HOA measurements taken during distance fixation. This does not point to an obvious underlying optical reason (i.e. reduced retinal image quality) for the more myopic eye typically being the dominant eye for higher levels of anisometropia. However, some

studies have reported that the non-dominant eye has a significantly higher level of astigmatism compared to the dominant eye, which increases with greater levels of anisometropia.^{31,189,193} While this suggests that image quality may play a role in the development of ocular dominance or anisometropia, the cross sectional nature of these studies prevents any firm conclusions regarding the causal nature of this association. One longitudinal study¹⁹⁰ examined the rate of myopia development between dominant and non-dominant eyes of young Asian myopes and concluded that sighting dominance has no influence upon refractive error development. However, this study only included isometric children (mean anisometropia 0.22 D, [range 0 - 1 D] at initial examination) and excluded moderate myopes, astigmatic myopes and children whose parents had myopia greater than -3.00 D, significantly reducing the likelihood of including participants who may have developed anisometropia.

Accommodation, binocularity and ocular dominance

Beyond a certain degree of anisometropia, the more myopic eye may be favoured for near work during binocular vision due to the reduced ocular accommodative demand relative to the fellow eye and thus dominates during binocular viewing. Studies of ocular changes of both eyes simultaneously during near tasks with binocular viewing may provide insight into characteristics that influence ocular dominance. Yang and Hwang¹⁹⁴ compared the interocular equality of the accommodative response in children with intermittent exotropia, without amblyopia or anisometropia. During monocular viewing, the dominant and non-dominant eyes of intermittent exotropes both showed a small lag of accommodation. However, during binocular fixation, a significant number of subjects displayed a greater lag of accommodation in the non-dominant eye compared to the fellow dominant eye. This finding suggests a potential mechanism for the non-dominant eye becoming more myopic (due to hyperopic defocus) compared to the dominant eye, in cases of atypical ocular alignment.

There is conflicting evidence regarding the association between the magnitude of myopic anisometropia and ocular dominance and its role, if any, in asymmetric refractive development. The fact that the more myopic eye is typically the dominant eye in some cohorts with higher levels of myopic anisometropia^{62,188} seems counterintuitive. In amblyopic eyes, the dominant eye is the eye with better visual acuity, which has experienced normal emmetropisation and has a lower degree of ametropia. Conversely, in non-amblyopic myopic anisometropia, initial reports suggested that the dominant eye tends to be the eye with the greater refractive error and further from emmetropia,^{62,188} but more recent findings from a much larger population³¹ suggests that the eye with the greater refractive error is typically the non-dominant eye, a trend which is amplified with increasing magnitude of anisometropia. One explanation may be that ocular dominance is predetermined genetically.¹⁹⁵ The eye which is then favoured for near work (as genetically determined) may be exposed to greater amounts of optical blur or mechanical stress resulting in greater axial elongation and myopia in the dominant eye causing anisometropia to develop. If this were the case, we might expect to see a greater lag of accommodation in the dominant eyes of anisometropes. An alternative explanation may be that ocular dominance is influenced by the development of anisometropia (particularly in Asian ethnicities). Beyond a certain degree of anisometropia, the more myopic eye may be favoured for near work during binocular vision due to the reduced ocular accommodative demand relative to the fellow eye and thus it may dominate during binocular viewing. This could explain why there is a significant shift to the more myopic eye as the dominant sighting eye when anisometropia exceeds 1.75 D in adult Asian myopes, but not children. To date, studies examining ocular dominance and anisometropia have been cross-sectional and have employed a simple forced choice method of determining sighting preference (the hole-in-the-card test¹⁹¹). A longitudinal study into the ocular changes of dominant and non-dominant eyes during the development of anisometropia (using more sophisticated techniques to quantify ocular dominance¹⁹⁶) may provide further

insight into the potential causal nature of this association. Characteristics of the dominant eye during binocular near work may help explain the underlying mechanism, if ocular dominance influences the development of myopic anisometropia. Apart from one study of myopic children,¹⁸⁹ the majority of adult subjects examined in other cohorts were presumably established anisometropes (i.e. not developing anisometropia). As such, we cannot rule out that visual acuity (or the quality of vision received) during anisometropia development plays a role in determining sighting dominance.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

A high degree of symmetry exists between the fellow eyes of myopic anisometropes for a range of biomechanical, biometric and optical parameters. To date, a single specific optical or mechanical factor has not been identified that is consistently associated with asymmetric axial elongation, but it is possible that there are many individual or combined stimuli that lead to a difference in eye growth between fellow eyes. The findings from the studies discussed in this review suggest many areas of potential interest that require further research.

There appears to be a strong association between ocular dominance and myopic anisometropia in Asian adults. A longitudinal study into the ocular changes of dominant and non-dominant eyes during anisomyopia development may provide further insight into the potential causal nature of this association. Characteristics of the dominant eye during binocular near work may also help to explain the underlying mechanism, if ocular dominance influences the development of myopic anisometropia. An interocular asymmetry in choroidal thickness has been observed that is proportional to the magnitude of anisomyopia. Previous animal studies have shown an active choroidal mechanism to emmetropise to imposed defocus^{118,187} and evidence for a similar mechanism in humans has recently been reported.¹²³ Given that the between eye differences in choroidal thickness cannot be explained by a simple passive stretch

model, interocular differences in myopiagenic stimuli may be driving asymmetric myopia development. Therefore, a longitudinal study examining factors such as the interocular symmetry of ocular biometry, optical quality (including corneal and total ocular astigmatism and higher order aberrations) and changes in the choroid during childhood-adolescent myopia development may provide important information regarding the development of asymmetric refractive errors.

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FIGURES

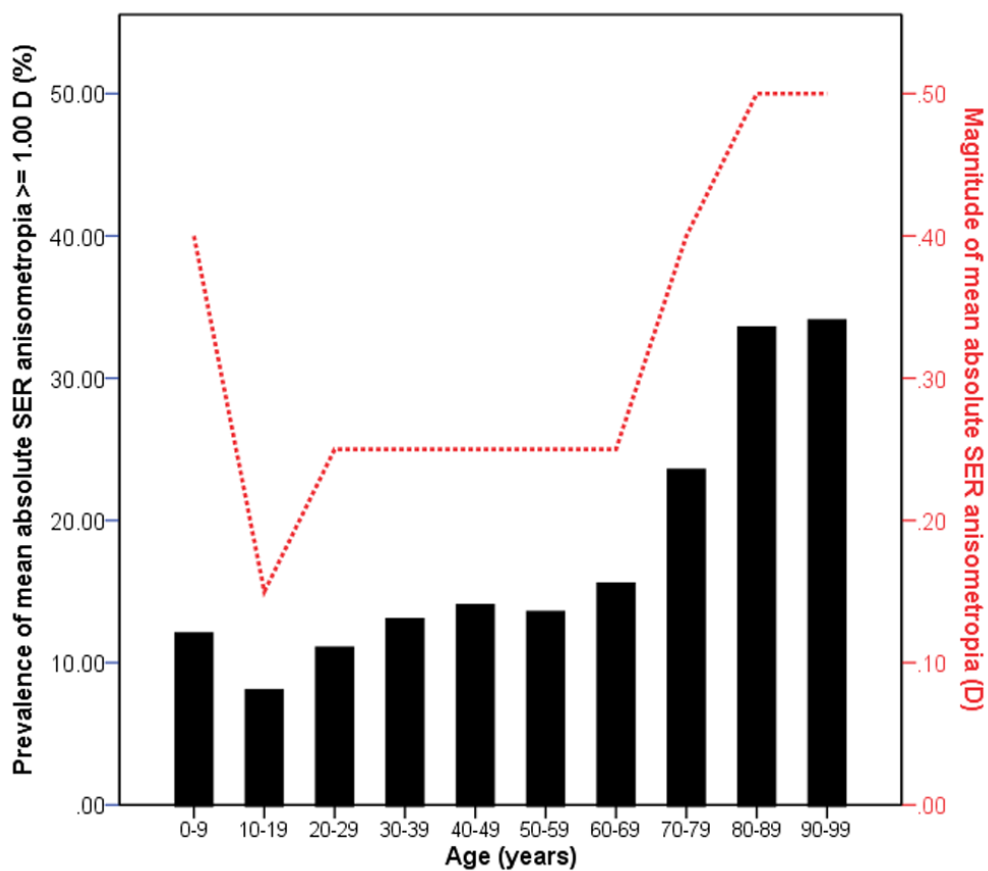


Figure 1. The prevalence and magnitude of anisometropia throughout life (based on data from a large clinical study of more than 85 000 patients including myopes, hyperopes, amblyopes and cases of ocular pathology⁹). The black bars represent the prevalence of mean absolute SER anisometropia ≥ 1.00 D (corresponding to the left y-axis). The red line represents the magnitude of mean absolute SER anisometropia, for all patients including isometropes and anisometropes (corresponding to the right y-axis). The prevalence and magnitude of anisometropia vary significantly over time.

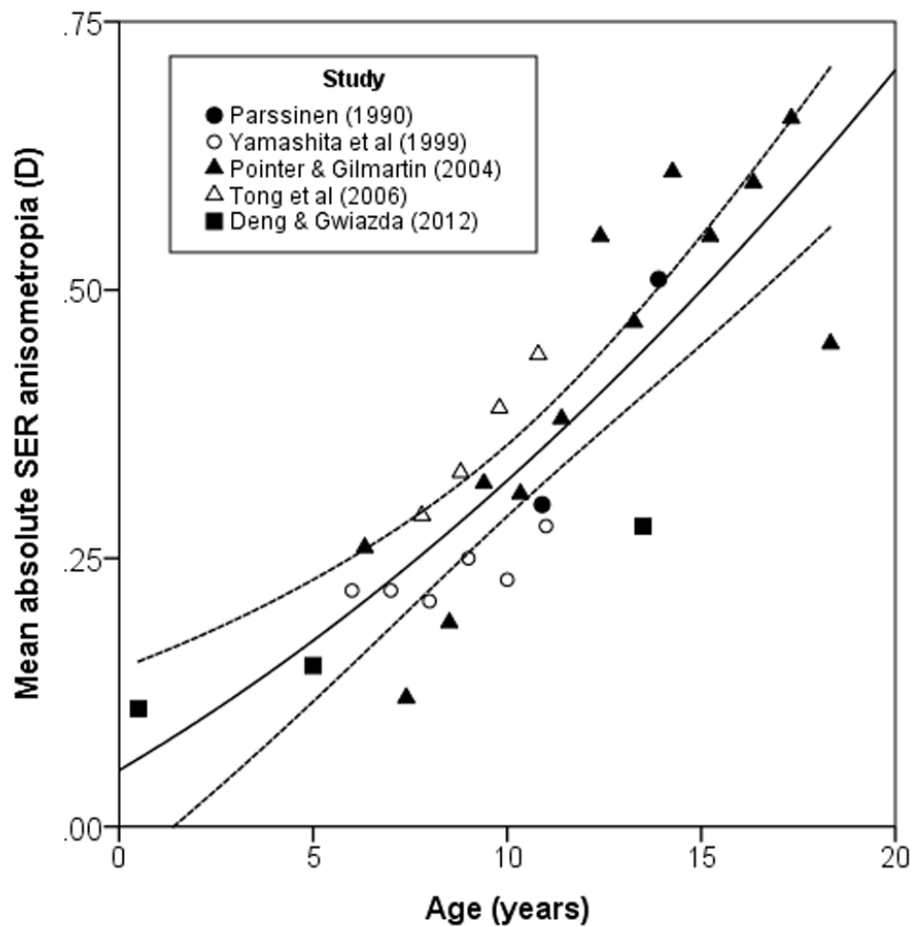


Figure 2: Combined data from longitudinal studies of non-amblyopic anisometropia throughout childhood and adolescence.¹⁹⁻²³ A small but significant increase in the magnitude of mean absolute SER anisometropia is observed with increasing age, which is associated with the progression of myopic and astigmatic refractive errors. Solid line represents the line of best fit and dotted lines 95% confidence intervals.

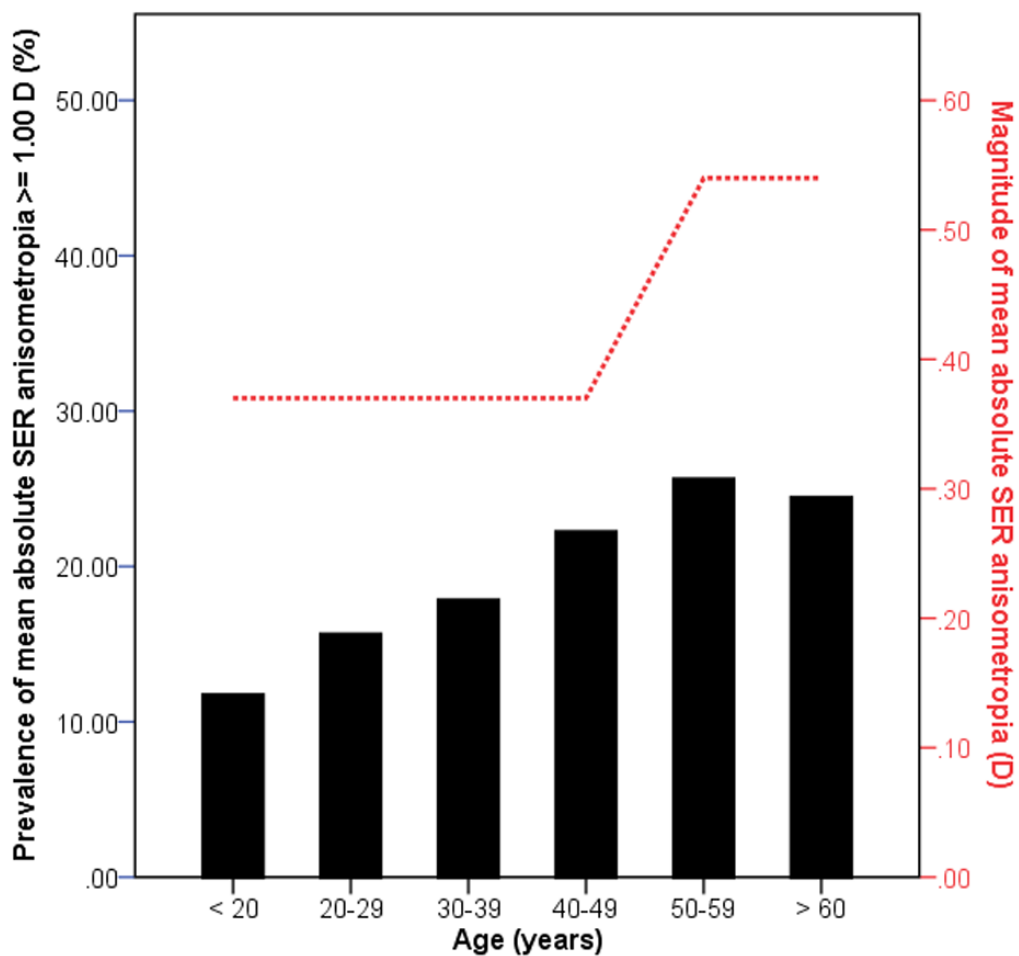


Figure 3. The prevalence and magnitude of anisometropia throughout life in myopia (based on data from a clinical study of refractive surgery candidates³¹). The black bars represent the prevalence of mean absolute SER anisometropia ≥ 1.00 D (corresponding to the left y-axis). The red line represents the magnitude of mean absolute SER anisometropia, for myopic patients only including myopic isometropes and anisometropes (corresponding to the right y-axis).

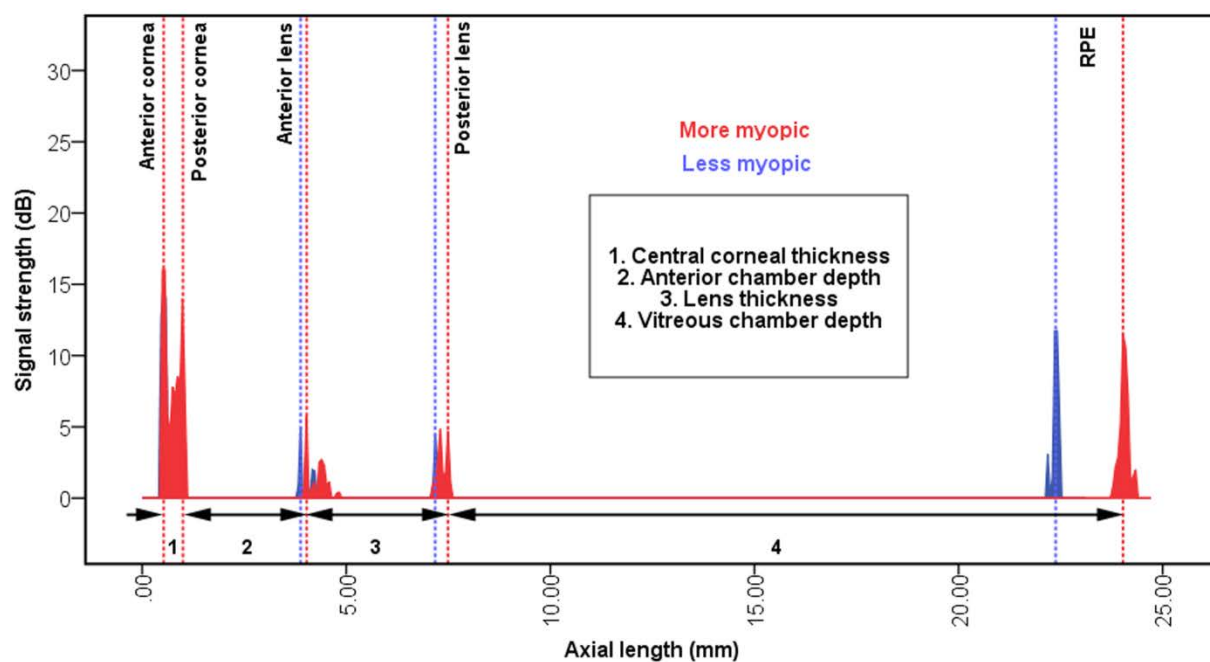


Figure 4. Optical low coherence reflectometry A-Scan output for the *more* myopic (RED, Axial length 24.70 mm, refraction -2.75/-1.75 x 5) and the *less* myopic (BLUE, Axial length 23.11 mm, refraction pl/-0.25 x 5) eyes of a typical non-amblyopic anisometrope. Biometric studies of anisometropic eyes have shown a high degree of symmetry is observed between the fellow eyes for measures of anterior segment structures. In this particular example; central corneal thickness (1) (*more* 501 μm , *less* 501 μm), anterior chamber depth (2) (*more* 3.12 mm, *less* 2.98 mm) and lens thickness (3) (*more* 3.53 mm, *less* 3.47 mm). The biometric basis of axial anisomyopia is the interocular difference in the vitreous chamber depth (4) (*more* 17.55 mm, *less* 16.15 mm). RPE – retinal pigment epithelium.

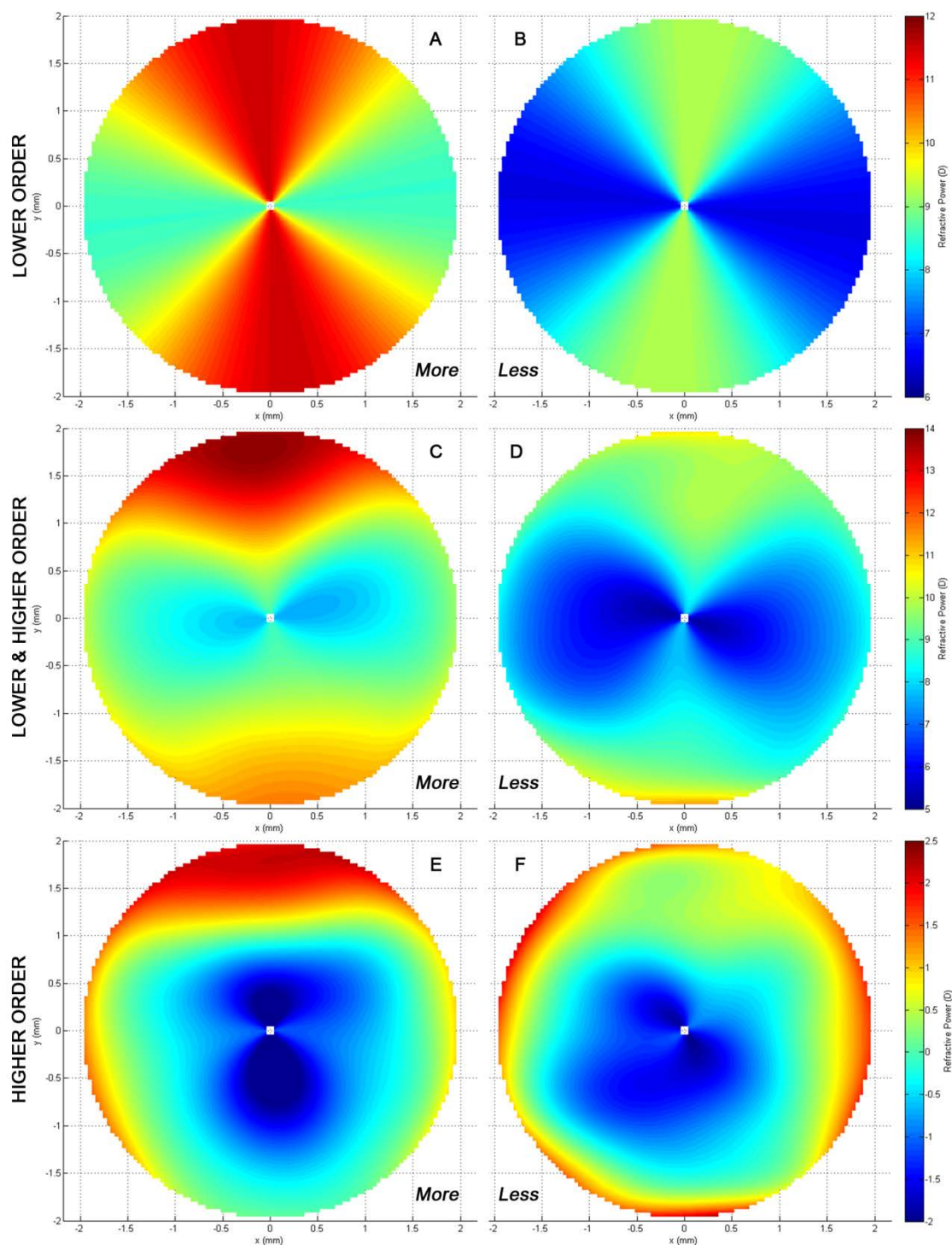


Figure 5: Mirror symmetry of astigmatism and comparison of higher order aberrations in a typical anisometric subject (R: $-4.25/-1.75 \times 15$ and L $-2.75/-1.75 \times 170$). The above refractive power maps (4 mm pupil) are generated from the total ocular wavefront for Zernike terms up to the 8th radial order: 4-6 (lower order terms, **A** and **B**), 4-45 (lower and higher order terms, **C** and **D**) and 7-45 (higher order terms only, **E** and **F**). Cross sectional studies of anisomyopes typically report similar levels of aberrations between the fellow eyes, or slightly higher levels in the less myopic eye.

Table 1: Summary of biometric studies of myopic anisometropia

Study	Cohort Criteria, Age, Mean Anisometropia, (n)		Method	IOD: <i>More minus Less myopic eye</i> (mm)					Note
				CCT	ACD	LT	VCD	AXL	
Sorsby et al (1962) ⁸ †	IOD vertical meridian ≥ 2.00 D		POP	—	- 0.06	+ 0.05	—	+ 2.66	Crystalline lens equivalent power; IOD in anisomyopia (-0.19 D) IOD in unilateral myopia (-0.67 D).
	Anisomyopia (23 \pm 12 years)	5.30 D, (27)							
	Unilateral myopia (23 \pm 15 years)	6.73 D, (8)		—	+ 0.04	+ 0.05	—	+ 3.81	
Logan et al (2004) ⁵⁸	Caucasian (18-26 years)	2.32 D, (14)	US	—	- 0.05	+ 0.01	+ 0.92*	+ 0.88*	Regional asymmetries (nasal – temporal) in peripheral IOD in AXL is more pronounced in Asian anisomyopes compared to Caucasians.
	Asian (14-26 years)	2.59 D, (14)		—	- 0.03	- 0.01	+ 1.33*	+ 1.29*	
Tong et al (2004) ⁵⁹	8 \pm 1 years		US	—	—	—	—	+ 0.21	IOD in AXL significantly greater in anisometropes compared to isometropes and weakly but significantly correlated with SER anisometropia ($r = 0.123$).
	Isometropes SER < 1.50 D, (1948)								
	Anisometropes SER ≥ 1.5 D, (31)			—	—	—	—	+ 1.14	
Huynh et al (2006) ⁶⁰	Anisometropia SER ≥ 1.00 D, (28)		OLCR (IOL)	—	0.10	—	—	0.72	Absolute IOD reported. IOD in ACD and AXL significantly different between anisometropes and isometropes.
	Anisometropia SER < 1.00 D, (1696)			—	0.05	—	—	0.09	
Kuo et al (2011) ⁶¹	29 anisomyopes, 20 antimetropes, 2 anisohyperopes		US	+ 0.005	+ 0.05	—	—	+ 1.6*	Presented thinnest corneal thickness, not CCT. The greater the magnitude of anisometropia, the greater the contribution of the IOD in AXL compared to ACD.
	23 \pm 2 years	4.87 D, (51)							
Vincent et al (2011) ⁶²	Anisomyopia (24 \pm 4 years)	1.70 D (34)	OLCR (IOL)	—	—	—	—	+ 0.57**	IOD in AXL significant correlation with SER anisometropia ($r = -0.81$).

Table 1 *continued*: Summary of biometric studies of myopic anisometropia

Study	Cohort		Method	IOD: <i>More minus Less myopic eye</i> (mm)					Note
	Criteria, Age, Mean Anisometropia, (n)			CCT	ACD	LT	VCD	AXL	
Kim et al (2013) ⁶³	SER ≥ 1.00 D	2.35 D, (5)	US	—	+ 0.13	- 0.12	+ 0.94	+ 0.93	IOD in VCD and AXL significantly correlated with magnitude of anisomyopia (both r = 0.96, p < 0.0001). On average, no significant IOD in ACD or LT.
		2.89 D, (11)		—	+ 0.09	0.00	+ 1.22	+ 1.32	
		4.86 D, (9)		—	+ 0.07	+ 0.04	+ 1.59	+ 2.80	
		7.12 D, (12)		—	+ 0.10	- 0.06	+ 2.69	+ 2.73	
		10.14 D, (7)		—	+ 0.32	- 0.27	+ 4.06	+ 4.10	
		15.29 D, (6)		—	+ 0.15	+ 0.01	+ 5.98	+ 6.14	
Vincent et al (2013) ⁶⁴	SER ≥ 1.00 D Anisomyopia		OLCR (LS)						ChT significantly thinner in more myopic eyes. Regional and ethnic variations in IOD of ChT.
	Caucasian (24 ± 7 years)	1.43 D, (10)		- 0.001	- 0.03	+ 0.02	+ 0.42*	+ 0.42*	
	Asian (23 ± 4 years)	2.09 D, (11)		0.000	+ 0.03	- 0.03	+ 0.67*	+ 0.77*	
Lin et al (2013) ⁶⁵	Anisomyopia (16 ± 5 years)	2.04 D, (43)	US	+ 0.001	+ 0.08	- 0.05	+ 0.77**	+ 0.79**	No significant difference in refractive astigmatism between the fellow eyes. NITM and its decay significantly greater in more myopic eye
Cho et al (2013) ⁶⁶	Anisomyopia (68 ± 2 years)	5.78 D, (34)	US	—	- 0.35*	+ 0.16	+ 0.02	+ 0.20	IOD LT (r = -0.70) and crystalline lens density (r = 0.79) highly correlated with magnitude of lenticular anisomyopia (p < 0.001).
	<i>Lenticular</i> only, not axial								

Table 1 continued: Summary of biometric studies of myopic anisometropia

Study	Cohort		Method	IOD: <i>More minus Less myopic eye (mm)</i>					Note
	Criteria, Age, Mean Anisometropia, (n)			CCT	ACD	LT	VCD	AXL	
O'Donoghue et al (2013) ⁶⁷	SER	7 years (33)	OLCR (IOL)	—	0.10	—	—	0.40	Data presented as absolute IOD. IOD in AXL significantly greater in anisometropes compared to isometropes. Degree of anisometropia correlated with IOD in AXL, not ACD or corneal ROC.
	Anisometropia ≥ 1.00 D	12 years (62)		—	0.10	—	—	0.60	
	SER	7 years (356)		—	0.10	—	—	0.10	
	Anisometropia < 1.00 D	12 years (559)		—	0.13	—	—	0.10	
	Aniso-astigmatism ≥ 1.00 D	7 years (30)		—	0.10	—	—	0.28	Data presented as absolute IOD. IOD in AXL significantly greater in aniso-astigmatism compared to iso-astigmatism. Risk of aniso-astigmatism greater in myopes compared with emmetropes.
		12 years (62)		—	0.11	—	—	0.33	
	Aniso-astigmatism < 1.00 D	7 years (356)		—	0.10	—	—	0.11	
		12 years (559)		—	0.13	—	—	0.14	

Positive values (+) indicate a larger measurement in the more myopic eye. **Bold** values indicate a significant interocular difference $p < 0.05$ (* $p < 0.001$, ** $p < 0.0001$).

† Authors reanalysis of Sorsby et al⁸ (excluding anisohyperopes and antimetropes).

ACD – anterior chamber depth, AXL – axial length, CCT – central corneal thickness, ChT – choroidal thickness, IOD – interocular difference, IOL – IOL Master (Zeiss), LS – LenStar biometer (Haag-Streit), LT – lens thickness, NITM – near work induced transient myopia, OLCR – optical low coherence reflectometry, POP – photographic ophthalmic phakometry, ROC – radius of curvature, RT – retinal thickness, US – A-scan ultrasonography, VCD – vitreous chamber depth.

Table 2. Summary of cross sectional studies of IOP in anisometric cohorts

Study	Age (years)	Anisometric cohort	Method	IOP (mean \pm SD) (mmHg)		Statistical significance		
				More myopic eye	Less myopic eye			
Tomlinson & Phillips (1972) ⁸⁷	8-16	Criteria not specified (n = 13)	GAT	14.0	13.3	p > 0.05		
Bonomi et al (1982) ⁸⁸	7-68	<i>Unilateral high myopia</i>						
		Myopic eye (SPH < -5.00 D) vs	GAT	16.1 \pm 2.6	16.4 \pm 2.4	p > 0.05		
		Fellow eye (EMM/HYP) (n = 42)	Schiotz	18.3 \pm 3.0	17.2 \pm 3.0	p < 0.05		
		<i>Anisomyopia</i>						
		More myopic eye (SPH < -5.00 D) vs Less myopic eye (-5.00 D < SPH < 0.00 D) (n = 95)	GAT Schiotz	16.1 \pm 2.5 17.8 \pm 3.3	16.8 \pm 2.3 17.1 \pm 3.0	p < 0.05 p < 0.05		
Mean anisometropia (all subjects): 11.15 D								
Shih et al (1991) ⁸⁹	18-58	< 1.00 D (n = 57)	GAT	Mean absolute interocular difference	1.14 \pm 1.30	p > 0.05		
		1.00 - 3.00 D (n = 49)			1.35 \pm 1.91	p > 0.05		
		> 3.00 D (n = 82)			1.34 \pm 1.24	p > 0.05		
Lee & Edwards (2000) ⁹⁰	8-14	SPH difference \geq 2.00D	NCT					
		<i>Anisomyopia cohort</i> : Mean 3.14 D (n = 24)			16.08 \pm 3.09	16.21 \pm 3.12	p = 0.65	
		<i>Antimetropia cohort</i> : Mean 4.24 D (n = 28)			16.86 \pm 3.60	17.11 \pm 3.45	p = 0.31	
Lam et al (2003) ⁹¹	20-34	SER \geq 2.00 D (n = 31), Mean 3.89 \pm 1.86 D	OBF		14.50 \pm 2.85	14.27 \pm 2.5	p = 0.41	
Xu et al (2010) ⁷⁹	18-56	More myopic eye SER < -8.00 D						
		Less myopic eye SER > -4.00 D (n = 23)			IOPg	14.0 \pm 3.8	13.5 \pm 3.6	p = 0.60
		Mean anisometropia 10.82 \pm 3.22 D			IOPcc	14.6 \pm 3.8	12.8 \pm 3.4	p = 0.07
Kuo et al (2011) ⁶¹	19-30	SPH difference \geq 4.00 D (n = 29) Mean anisomyopia 4.59 D	NCT	Mean interocular difference	1.00 (95% CI 0.3 - 1.9)	p = 0.004		
Vincent et al (2011) ⁶²	18-34	SER \geq 1.00 D (n = 31)	IOPg		15.60 \pm 2.98	15.66 \pm 2.86	p = 0.83	
		Mean 1.70 \pm 0.74 D	IOPcc		15.05 \pm 2.20	15.15 \pm 2.14	p = 0.66	

Bold values indicate a statistically significant interocular difference (or borderline). EMM (emmetropia), GAT (Goldmann applanation tonometry), HYP (hyperopia), IOPcc – Corneal compensated IOP, IOPg – Goldmann correlated IOP, NCT (non contact tonometry), OBF (ocular blood flow tonometry), SER (spherical equivalent refraction), SPH (spherical component of refraction).

Table 3: Summary of cross sectional studies of corneal power (or radius of curvature) in anisometropia

Study	Cohort: Criteria, Age, Mean Anisometropia, (n)	Method	IOD in Corneal Power (D)/ROC (mm)	Other	
Sorsby et al (1962) ⁸ †	IOD vertical meridian ≥ 2.00 D	POP		No correlation between IOD corneal power and anisometropia in anisomyopes ($r = 0.04$), but moderate correlation in unilateral myopes ($r = 0.75$).	
	Anisomyopia (23 ± 12 years)		5.30 D, (27)		+ 0.02 D
	Unilateral myopia (23 ± 15 years)		6.73 D, (8)		+ 0.00 D
Logan et al (2004) ⁵⁸	Caucasian (18-26 years)	Keratometry	ROC: 0.00 mm	No anterior segment contribution to anisomyopia in Asians or Caucasians	
	Asian (14-26 years)		2.59 D, (14)		ROC: - 0.02 mm
Tong et al (2004) ⁵⁹	8 \pm 1 years	Autokeratometry		Reported right minus left eye (absolute) not more minus less myopic. No significant difference in IOD between isometric and anisometric children.	
	Isometropes SER < 1.50 D, (1948)				Absolute difference 0.24 D
	Anisometropes SER ≥ 1.5 D, (31)				Absolute difference 0.37 D
Huynh et al (2006) ⁶⁰	Anisometropia ≥ 1.00 D, (28)	OLCR (IOL)	Absolute difference 0.28 D	IOD in corneal power not significantly different between anisometropia and isometropia.	
	Anisometropia < 1.00 D, (1696)		Absolute difference 0.22 D		
	Aniso-astigmatism ≥ 1.00 D, (17)		Absolute difference 0.87 D	Aniso-astigmatism is related to corneal, not internal astigmatism.	
	Aniso-astigmatism < 1.00 D, (1707)		Absolute difference 0.23 D		
Kuo et al (2011) ⁶¹	29 anisomyopes, 20 antimetropes, 2 anisohyperopes	Orbscan		Mean simulated K reading ($p = 0.15$). No significant interocular difference in WTW dimensions.	
	23 \pm 2 years		4.87 D, (51)		+ 0.11 D
Kim et al (2013) ⁶³		Keratometry	2.35 D, (5)	+ 0.14 D	
	IOD ≥ 1.50 D		2.89 D, (11)	+ 0.13 D	
	Anisomyopia (36 ± 15 years)		4.86 D, (9)	+ 0.04 D	
	Included 12 amblyopes		7.12 D, (12)	+ 0.01 D	
			10.14 D, (7)	+ 0.17 D	
			15.29 D, (6)	- 0.09 D	
Vincent et al (2011) ⁶²	Anisomyopia (24 ± 4 years) SER ≥ 1.00 D	Medmont	Flat: + 0.14 D*, Steep: + 0.20 D Mean: + 0.17 D **	No significant difference in refractive astigmatism between fellow eyes. Average corneal asphericity (Q) values were slightly more prolate (greater peripheral flattening) in the more myopic eye.	
Lin et al (2013) ⁶⁵	Anisomyopia (16 ± 5 years) SER > 1.00 D	Autokeratometry	ROCh: - 0.04 mm* ROCv: + 0.01 mm	No significant difference in refractive astigmatism between the fellow eyes.	
Cho et al (2013) ⁶⁶	Anisomyopia (68 ± 2 years) Lenticular only, not axial	Scheimpflug	- 0.02 D	Denser nucleus and thinner lens (greater asymmetry in lenticular refractive index) responsible for age-related lenticular anisomyopia.	

Table 3 continued: Summary of cross sectional studies of corneal power (or radius of curvature) in anisometropia

Study	Cohort: Criteria, Age, Mean Anisometropia, (n)	Method	IOD in Corneal Power (D)/ROC (mm)	Other
O'Donoghue et al (2013) ⁶⁷	Anisometropia ≥ 1.00 D	OLCR (IOL)	7.1 years, 8.5% (33)	Data presented as absolute IOD. No significant IOD in corneal ROC in anisometric or isometric children.
			0.04 mm	
			12.1 years, 9.4% (62)	0.05 mm
	Aniso-astigmatism ≥ 1.00 D		7.1 years, 7.7 % (30)	0.83 D
	12.1 years, 5.6 % (62)	0.76 D		

* $p < 0.05$, ** $p < 0.01$

† Authors reanalysis of Sorsby et al⁸ (excluding anisohyperopes and antimetropes).

IOD – interocular difference, OLCR (IOL) – Optical low coherence reflectometry, IOL Master (Zeiss), POP – photographic ophthalmic phakometry, ROC – radius of curvature, WTW – white to white.

Table 4: Summary of studies of accommodation in myopic anisometropia

Study	Cohorts examined	Method	Results	Note
Hosaka et al (1971) ¹⁵³	Isometropia (n = 94), 0-50 years Anisometropia (n = 98), 0-40 years (≥ 1.00 difference in refraction, range 1-7 D)	"Monocular near point of accommodation using the Ishihara near point scale"	97% of isometropes with IOD AA < 2.00 D compared with 69% of anisometropes.	Authors consider near point of accommodation test limited to 0.50 D accuracy. Inclusion of amblyopic anisometropes may confound results.
Xu et al (2009) ¹⁵⁴	Iso-emmetropia (n = 20), 20-31 years (SER +0.37 to -0.25 D in both eyes) Anisometropia (n = 20) (2.50 - 7.00 D SPH)	Grand Seiko WV-500 optometer Binocular viewing with CL correction 1, 2, 3, & 4 D stimuli	No significant difference between fellow eyes in anisometropia for all accommodation demands. For 3 & 4 D stimuli, more myopic eye of anisometropes significantly greater lag compared to emmetropes.	Overall trend for lag of accommodation; More myopic eye > Less myopic eye > Iso-emmetropic eyes (But not statistically significant).
Lin et al (2013) ⁶⁵	Anisomyopia (n = 43), 15.7 \pm 5.4 years (SER anisometropia > 1.00 D, mean 2.04 D) No amblyopic or strabismic participants	Grand Seiko WAM-5500 autorefractor Non-cycloplegic autorefraction measured pre and post near task (5 minutes, 5 D demand).	NITM and decay time significantly greater in more myopic (0.21 D, 108 s) eye compared to less myopic eyes (0.15 D, 87 s) ($p < 0.05$).	Moderate correlation between the IOD in NITM decay area and the magnitude of SER anisometropia ($r = 0.31$, $p < 0.05$).

AA – amplitude of accommodation, CL – contact lens, IOD – interocular difference, NITM – near work induced transient myopia, SER – spherical equivalent refraction, SPH – spherical component anisometropia

Table 5: Summary of studies of higher order aberrations in anisometropia

Study	Anisometropia	Cohort	Technique	Results
Corneal HOA				
Vincent et al (2011) ⁶²	SER \geq 1.00 D	34 anisomyopes	Medmont E300 corneal height data, translated to the line of sight. 4 & 6 mm corneal diameters.	No significant interocular differences between the fellow eyes for 3 rd , 4 th and total corneal HOA (slightly higher in less myopic eyes).
	Mean 1.70 \pm 0.74 D	23.9 \pm 4.3 years		
Vincent et al (2013) ¹⁴⁰	SER \geq 1.00 D	34 anisomyopes	Pre and post reading Medmont E300 corneal height data, translated to the line of sight 4 & 6 mm corneal diameters.	Symmetrical change in corneal HOA profile following a reading task. Significantly greater change in corneal astigmatism in the more myopic eye over 6mm diameter.
	Mean 1.70 \pm 0.74 D	23.9 \pm 4.3 years		
Total ocular HOA				
Kwan et al (2009) ¹⁶⁵	SER \geq 2.00 D	26 anisomyopes	H-S aberrometer (COAS) Natural pupils, 5mm analysis diameter Distance fixation	Less myopic eyes significantly more aberrated: 3 rd order RMS: <i>Less</i> 0.201 μ m, <i>More</i> 0.157 μ m ($p < 0.05$) C (4,0): <i>Less</i> 0.108 μ m, <i>More</i> 0.088 μ m ($p < 0.01$) Total HOA RMS: <i>Less</i> 0.245 μ m, <i>More</i> 0.200 μ m ($p < 0.05$)
	Mean: 3.40 D	29.4 (range 19-48) years		
Tian et al (2011) ¹⁶⁶	SER > 1.00 D	15 anisomyopes 23.87 \pm 3.52 years	H-S aberrometer (COAS) Dilated pupils, 5 mm analysis diameter Distance fixation	No significant between fellow eyes or between group (Iso vs Aniso) differences in HOA (3 rd to 5 th order and total HOA).
	Mean: 1.73 \pm 0.67 D	16 isomyopes Mean: 0.14 \pm 0.27 D		
Vincent et al (2011) ⁶²	SER \geq 1.00 D	34 anisomyopes	H-S aberrometer (COAS) Natural pupils, 4 & 6 mm analysis diameters Distance fixation	No significant interocular differences between the fellow eyes for 3 rd , 4 th order terms and total corneal HOA (slightly higher in less myopic eyes).
	Mean 1.70 \pm 0.74 D	23.9 \pm 4.3 years		
Hartwig & Atchison (2012) ¹⁶⁷	SER > 2.00 D	614 anisomyopes. Age, amblyopia, pathology and surgical status unknown.	H-S aberrometer (i.Profiler) Pupil status unknown, 4.5 mm analysis diameter Internal fixation target	Examined the relationship between the coefficient of each aberration term (up to the 4 th order) as a function of SER for the more and less myopic eyes. Significant between eye difference in slope and intercept for trefoil term.
	Range 2 – 10 D			
Hartwig et al (2013) ¹⁶⁸	SER \geq 1.00 D	20 anisomyopes/hyperopes 43 \pm 17 years	H-S aberrometer (i.Profiler) Pupil status unknown, 4 mm analysis diameter Internal fixation target	In general, a higher degree of interocular symmetry in the anisometropic group compared to isometropic control group (up to 4 th order). Analysis conducted as right vs left eye comparison instead of more vs less ametropic eye.
	Mean: 2.81 \pm 2.04 D	20 isometropes Mean 0.28 \pm 0.21 D		

C(4,0) – Zernike coefficient spherical aberration, COAS – Complete Ophthalmic Analysis System (Wavefront Sciences), HOA – higher order aberrations, H-S – Hartmann Shack, i.Profiler (Carl Zeiss), RMS – root mean square error, SER – spherical equivalent refraction.

Table 6: Summary of studies of ocular sighting dominance and refractive error

Study	Anisometropia	Participants	Method	Result	Note
Cheng et al (2004) ¹⁸⁸	≥ 0.5 D SER	Adult anisomyopes Mean age 30 ± 10 years Taiwanese, n = 55	HIC, NPT	> 1.75 D anisometropia, dominant eye significantly more myopic (~3 D, p < 0.001).	Authors suggest an influence of an aniso-accommodative response
Chia et al (2007) ¹⁸⁹	≥ 0.50 D SER	Data from 5 th annual review in SCORM 14-year-old children Chinese, n = 162	HIC	≥ 1.75 D anisometropia, dominant eye more myopic in only 56% (p > 0.05).	Greater astigmatism in the non-dominant eye (~0.20 D, p < 0.001)
Yang et al (2008) ¹⁹⁰	≤ 1.00 D	7-13 year old myopes (-0.50 to -3.00 D) Mean anisometropia 0.22 D Chinese, n = 130	HIC	No effect of ocular dominance on refractive development over two years.	Excluded children with: myopia > 3.00D, astigmatism > 1.50 D and parental myopia > -3.00 D.
Vincent et al (2011) ⁶²	≥ 1.00 D SER	Adult anisomyopes Mean age 24 ± 4 years Predominantly South East Asian, n = 34	HIC	> 1.75 D anisometropia, dominant eye more myopic eye in 90% (p < 0.05).	Similar levels of corneal and total HOA in dominant and non-dominant eyes (p > 0.05).
Linke et al (2011) ³¹	≥ 2.50 D SER	Non-amblyopic myopic anisometropes Mean age 35 ± 9 years European clinic sites, n = 278*	HIC	≥ 2.50 D SER, non-dominant eye more myopic in 64% (p < 0.001).	Interocular difference in astigmatism > 0.50 D, non-dominant eye more astigmatic (p < 0.001).

HIC – hole-in-the-card test, HOA – higher order aberrations, NPT – near point test, SER – spherical equivalent refraction, SCORM - Singapore Cohort Of the Risk factors for Myopia study